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(54) Title: PROCESS FOR PREPARING PIPERAZIC ACID AND ITS CONVERSION TO N-ACYLATED BICYCLIC RINGS CONTAINING N,N-LINKAGES USEFUL AS INTERMEDIATES FOR CASPASE INHIBITORS			
(57) Abstract The invention relates to a process for synthesizing piperazic acid and similar, ring-containing acids. The invention also relates to a process for simultaneously N(2)-acylating piperazic acid or an ester thereof and forming a bicyclic ring structure. The invention also relates to the use of either or both processes in a method of synthesizing a bicyclic compound useful as an intermediate for the production of an inhibitor of a caspase, particularly an inhibitor of interleukin- β converting enzyme ("ICE").			

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PROCESS FOR PREPARING PIPERAZIC ACID AND ITS CONVERSION TO N-ACYLATED BICYCLIC RINGS
CONTAINING N,N-LINKAGES USEFUL AS INTERMEDIATES FOR CASPASE INHIBITORS

5 AN INTERMEDIATE IN THE MANUFACTURE OF A CASPASE INHIBITOR

TECHNICAL FIELD OF THE INVENTION

The invention relates to a process for synthesizing piperazic acid and similar, ring-containing
10 acids. The invention also relates to a process for simultaneously N(2)-acylating piperazic acid or an ester thereof and forming a bicyclic ring structure. The invention also relates to the use of either or both processes in a method of synthesizing a bicyclic compound
15 useful as an intermediate for the production of an inhibitor of a caspase, particularly an inhibitor of interleukin-1 β converting enzyme ("ICE").

BACKGROUND OF THE INVENTION

Piperazic acid derivatives are important
20 intermediates in natural product synthesis and in the synthesis of biologically useful non-natural amino acids and peptidomimetics (e.g., inhibitors described in PCT publications WO 97/22619 and WO 95/35308). Several syntheses of piperazic acid and derivatives thereof have
25 been described [Decicco et al., Syn. Lett., p. 615 (1995); Schmidt et al., Synthesis, p. 223 (1996); Rutjes et al., Tetrahedron, p. 8605 (1993); PCT publications WO 97/22619 and WO 95/35308). In each case however, the synthesis requires multiple steps, utilizes expensive
30 reagents and produces less than desirable yields.

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Compounds containing a bicyclic, aza-containing ring systems have been prepared as conformationally restricted dipeptide surrogates for a variety of medically important compounds. In particular, such ring systems are present in angiotensin converting enzyme (ACE) inhibitors, such as Cilazapril®, and in caspase inhibitors, such as inhibitors of interleukin-1 converting enzyme (ICE).

Current methods for synthesizing compounds containing these bicyclic aza-containing ring systems have many disadvantages. The typical methods of forming this ring system have been described [EP 94,095, WO 95/35308, WO 97/22619, United States patents 5,656,627, 5,716,929 and 5,756,486 and J. P. Kim, et al., Tetrahedron Letters, 38, pp. 4935-4938 (1997)].

These methods involve coupling an appropriately protected amino acid with the appropriately N(1)-protected piperazic acid or ester. After deprotection, the bicyclic system is then formed via an acid chloride coupling at the N(1) position.

The main disadvantages to such methods are the use of expensive reagents and the number of steps required for protection and deprotection making the overall process extremely time consuming. Moreover, these methods are often useful for research purposes but are not amenable to large scale production.

In order to be more commercially feasible, it would be desirable to produce compounds containing a bicyclic aza-containing ring system in an easier, less expensive manner than has been previously described.

SUMMARY OF THE INVENTION

Applicant has solved the problems indicated above by providing: 1) a new method for synthesizing
5 piperazic acid; and 2) a new method of simultaneously
N(2)-acylating an N(1)-protected piperazic acid or an
ester thereof and creating a bicyclic ring structure
comprising that acylated piperazic acid or ester.

The first method involves treating a 1,4-
10 dihaloalkyl ester with an N,N'-bis-protected hydrazine
dissolved in DMF in the presence of a water scavenger, a
metal hydroxide and a phase transfer catalyst. This
method produces surprisingly increased yield of the
desired protected piperazic acid.

15 The second method involves the formation of the
desired bicyclic system in two, simple steps. This
method also utilizes inexpensive reagents, does not
require selective protection/deprotection, and is quite
amenable to large scale production. Moreover, this
20 method produces very little contaminating by-products.
This method also preserves chirality between the N(1)-
protected piperazic or similar acid or an ester thereof
and the resulting bicyclic aza-containing ring system.

This method is particularly useful for
25 producing an intermediate that may be subsequently
converted into a caspase inhibitor, particularly an
inhibitor of ICE, through additional steps known in the
art.

DETAILED DESCRIPTION OF THE INVENTION

Some of the abbreviations used throughout the specifications (including in chemical formulae) are:

Bu = butyl

5 Et = ethyl

Cbz = carboxybenzyl

DMF = N,N-dimethylformamide

THF = tetrahydrofuran

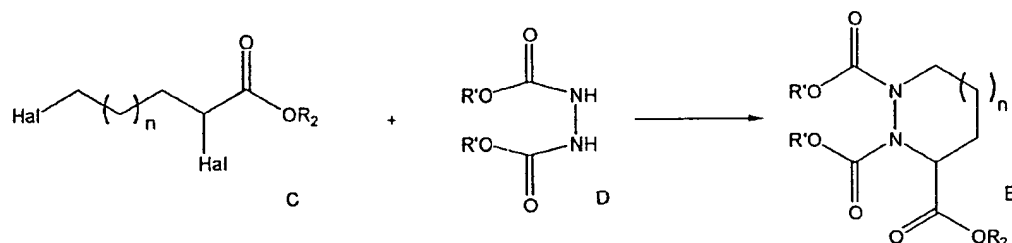
MTBE = methyl tert-butyl ether

10 DCC = dicyclohexyl carbodiimide

EDC = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride

Ac = acetyl.

According to one embodiment, the invention
15 provides a process for producing compound E by reacting
compounds C and D:



comprising the steps of:

- a) dissolving compounds C and D together in DMF;
- 20 b) adding to said solution of C and D:
 - i) a water scavenger;
 - ii) a metal hydroxide selected from LiOH, NaOH or KOH; and
 - iii) a phase transfer catalyst
- 25 c) allowing the mixture produced in step b) to react at room temperature for 2 to 48 hours;

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- d) adding an organic solvent and water to said mixture to create an aqueous phase and an organic phase; and
- e) purifying compound E from said organic phase;

5 wherein:

R₂ is selected from hydrogen, C1-C6 straight or branched alkyl; C2-C6 straight or branched alkenyl or alkynyl C1-C6 alkyl or Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar;

10 n is 0 or 1;

"Hal" is any halogen; and

each R' is an independently selected carboxyl protecting group

The water scavenger referred to above may be
15 selected from any water scavengers known in the art. These include, but are not limited to, Na₂SO₄, MgSO₄, and molecular sieves. Preferably, the water scavenger is sodium sulfate.

According to another preferred embodiment, the
20 metal hydroxide used in the above method is LiOH.

The phase transfer catalyst referred to in the above method may also be selected from any such catalysts known in the art. These include, but are not limited to, Bu₄NI, Aliquat 336 (Aldrich Chemicals) and other
25 quartenary ammonium salts. Preferably, the catalyst is Bu₄NI.

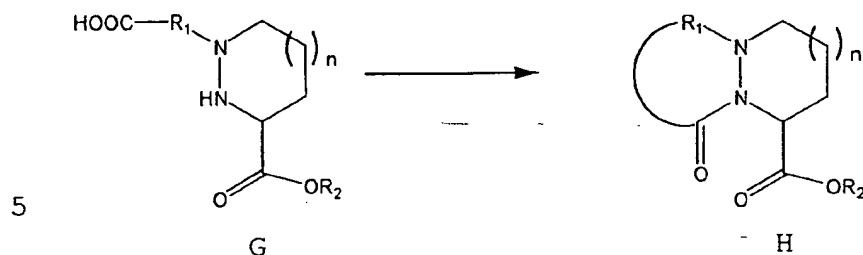
According to another preferred embodiment, n is
1.

According to yet another preferred embodiment,
30 each Hal is Br.

In yet another preferred embodiment of the method set forth above, R₂ is t-butyl.

In another preferred embodiment, R' is benzyl.

According to another embodiment, the invention provides a process for converting compound G to compound H:



wherein:

R₁ is a C2-C4 straight chain alkyl optionally substituted at any carbon with one or more substituents selected from C1-C6 straight or branched alkyl, C2-C6
10 ~~straight or branched~~ alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl or alkynyl, oxo, halo, NO₂, N(R₄)(R₄), CN, Ar or O-Ar;

R₂ is selected from hydrogen, C1-C6 straight or
15 branched alkyl, C2-C6 straight or branched alkenyl or alkynyl C1-C6 alkyl or Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar;

n is 0 or 1;

Ar is a saturated, partially saturated or
20 unsaturated monocyclic or bicyclic ring structure, wherein each ring contains 5 to 7 ring atoms and each ring optionally contains from 1 to 3 heteroatoms selected from O, N and S;

wherein Ar is optionally substituted at one or more
25 ring atoms with one or more substituents independently selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl

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or alkynyl, oxo, halo, NO₂, N(R₄)(R₄), CN, Ar₁, O-Ar₁;
wherein

Ar₁ is a saturated, partially saturated or
unsaturated monocyclic or bicyclic ring structure,
5 wherein each ring contains 5 to 7 ring atoms and each
ring optionally contains from 1 to 3 heteroatoms selected
from O, N and S; and

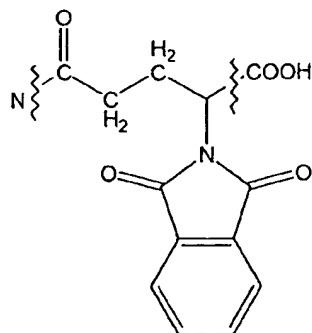
each R₄ is independently selected from H or an amino
protecting group, with the proviso that both R₄ are not
10 simultaneously hydrogen.

The term "amino protecting group", as used
herein, means a moiety that prevents chemical reactions
from occurring on the nitrogen atom to which that
protecting group is attached. An amino protecting group
15 must also be removable by a chemical reaction.

In one preferred embodiment, R₁ is substituted
at the terminal carbon bound to the -COOH moiety with a
protected amine. The term "protected amine" as used
herein, means a nitrogen-containing moiety which can be
20 chemically modified to an amine.

In another preferred embodiment, R₁ is
substituted at the other terminal carbon (i.e., the one
bound to the ring nitrogen) with oxo, making R₁ an acyl-
containing moiety. More preferred is when R₁ contains
25 both the protected amine substituent and the oxo
substituent. One of the most preferred R₁ groups is:

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In another preferred embodiment, n is 1.

In yet another preferred embodiment, R_2 is t-
 5 butyl.

The method of this invention comprises the
 steps of:

- (a) suspending compound G in an organic solvent
 selected from dichloroethane, dichloromethane,
 10 toluene, chlorobenzene, chloroform, monoglyme,
 diglyme or CCl_4 ;
- (b) adjusting the temperature of the resulting
 solution to between 20°C and 100°C ;
- (c) adding base and more than about 1 equivalent of
 15 RSO_pCl_p to said solution, wherein R is absent or
 is selected from C1-C6 straight or branched
 alkyl or Ar, and each p is independently 1 or
 2; and
- (d) allowing the reaction to proceed over a period
 20 of between 2 and 24 hours.

Not all organic solvents may be used to
 dissolve compound G in step (a). The list of solvents
 set forth above are known to work. Other similar organic
 solvents may also work in the reaction and are to be
 25 considered part of the present invention. Preferably,
 the organic solvent is toluene or dichloroethane.

Step (b) is preferably carried out at about 70°C.

According to a alternate embodiment, in step (c), less than about 0.2 equivalents of N,N-dimethylformamide may also added.

In another preferred embodiment of step (c), RSO_pCl_p is selected from methanesulfonyl chloride or SOCl_2 . Preferably, in step (c), about 1 to 3 equivalents of RSO_pCl_p are added.

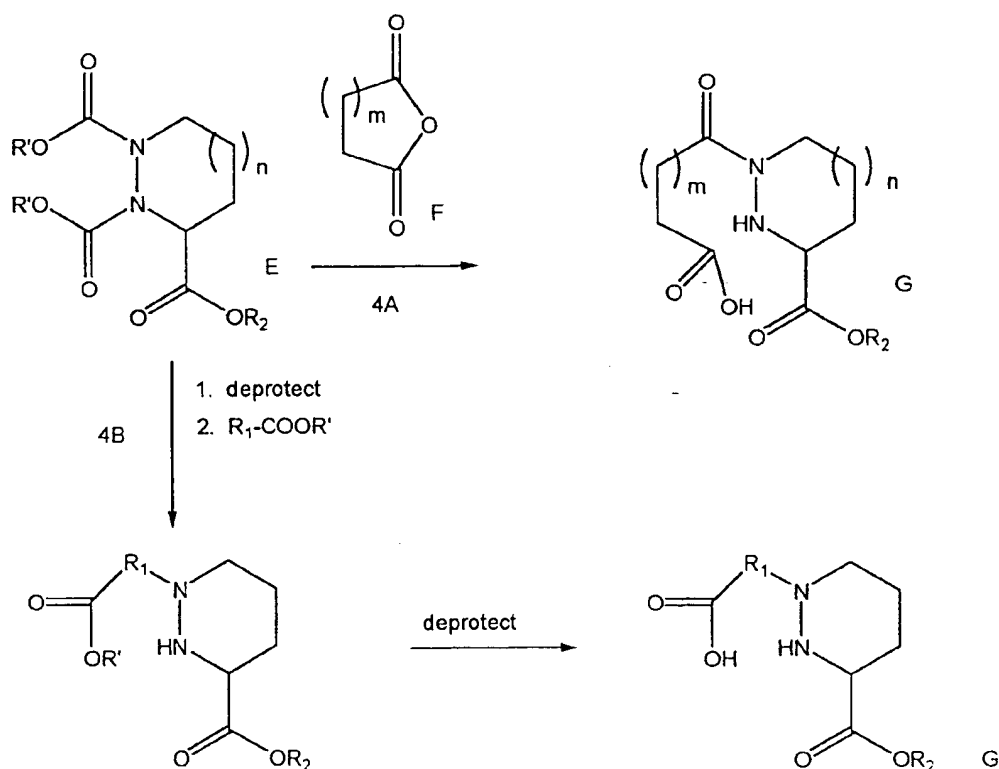
According to yet another preferred embodiment of step (c), about 2 to 4 equivalents of base are added to the reaction. Preferably, the base is selected from pyridine, collidine, lutidine, NaHCO_3 , imidazole, triethylamine, N-methylmorpholine, diisopropylethylamine or K_2CO_3 . Most preferably, the base is 2,6-lutidine.

In step (c), the base and the RSO_pCl_p are added simultaneously and may be added all at once to the reaction or gradually over period of time up to 3 hours.

Once the reaction is complete, we prefer to purify compound H by diluting the reaction with an organic solvent and then washing the solution first with NaHCO_3 and then with brine. The solution is then dried over Na_2SO_4 and concentrated.

Compound G may be obtained from compound E. That conversion may be achieved in one of two ways depicted below in Scheme 2, depending upon the nature of R_1 .

Scheme 1



In Scheme 1, m is 0, 1 or 2; and n , R' , R_1 and R_2 are as defined above. Also, in compound F any of the

5 unsubstituted ring carbon atoms may be optionally substituted by one or more substituents independently selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl

10 or alkynyl, oxo, NO_2 , $\text{N}(\text{R}_4)(\text{R}_4)$, CN, Ar, or O-Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar, and wherein R_4 and Ar are as defined above.

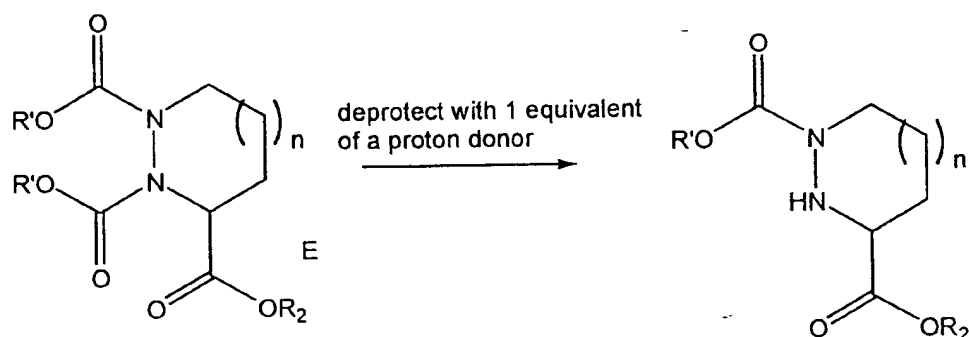
Reaction 4A comprises stepwise deprotection and acylation (which can be performed in the same reaction

15 vessel) if the carboxyl protecting groups can be removed by hydrogenolysis, (e.g., if the protecting group is benzyl) or utilizing transfer hydrogenation conditions.

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If not, a deprotection step must precede the addition of the anhydride for the acylation reaction.

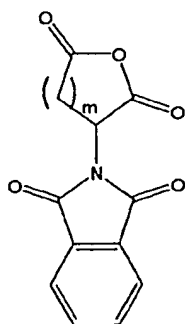
In order to completely deprotect at both nitrogens under transfer hydrogenation conditions, at least 2 equivalents of the proton donor (e.g., Et_3SiH) must be added. If only one equivalent of the proton donor is added, deprotection occurs selectively at the N(2) nitrogen:



10 The resulting N(1) protected compound is also useful as an intermediate in producing medically important compounds, such as the ICE inhibitors described herein and in PCT publications WO 97/22619 and WO 95/35308. Thus, this reaction to produce an N(1) protected compound
15 is also an embodiment of the present invention.

When compound F contains substituents and is not symmetrical, reaction 4A produces mixtures of compounds, wherein acylation of the N(1) nitrogen may occur at either C(O) functionality. This may be avoided
20 by using substituents that favor the formation of the desired product. For example, in reaction 4A, the use of:

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as compound F forces the formation of a compound wherein acylation of the N(1) nitrogen occurs at the C(O) functionality furthest away from the phthalimide substituent.

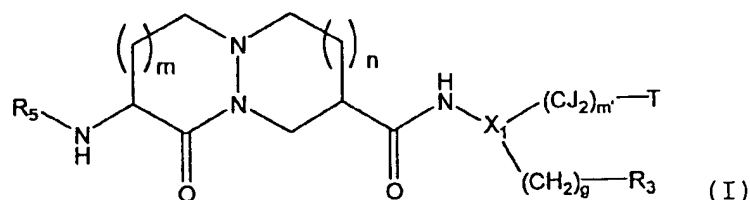
5 In order to avoid an unwanted reaction at the N(2) nitrogen in step 4B, the two carboxy protecting groups (R') on compound E should be different, such that the N(1) protecting group (-COOR') can be selectively removed without removing the N(2) protecting group.

10 The creation of intermediate E can be achieved by standard syntheses known in the art. More preferably, intermediate E is synthesized by reacting compounds C and D according to the method of this invention as set forth above.

15 Intermediate compound G containing the protected amine on R₁, and its subsequent conversion to compound H, may serve as the key intermediate and synthesis step, respectively, in an improvement in the synthesis of known caspase inhibitors, particularly
 20 inhibitors of interleukin-1 converting enzyme ("ICE"), such as those described in United States patents 5,716,929, 5,656,627, and 5,756,466 and in PCT publications WO 95/35308 and WO 97/22619.

Those inhibitors have the general formula (I):

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wherein:

any ring is optionally substituted at any carbon by Q₁, at any nitrogen by R₅, and at any atom by =O, -OH,

5 -COOH, or halogen;

X₁ is CH or N;

g is 0 or 1;

m and m' are independently 0, 1 or 2;

n is 0 or 1;

10 each J is independently selected from -H, -OH, or -F, provided that when a first and a second J are bound to a C, and said first J is -OH, then said second J is -H;

15 T is -Ar₃, -OH, -CF₃, -C(O)-C(O)-OH, -C(O)-OH or any biosteric replacement for -C(O)-OH;

R₃ is -CN, -CH=CH-R₉, CH=N-O-R₉, -(CH₂)₁₋₃-T₁-R₉, -CJ₂-R₉, -C(O)-R₁₃, or -C(O)-C(O)-N(R₅)(R₁₀);

20 T₁ is -CH=CH-, -O-, -S-, -SO-, -SO₂-, -NR₁₀-, -NR₁₀-C(O)-, -C(O)-, -O-C(O)-, -C(O)-O-, -C(O)-NR₁₀-, O-C(O)-NR₁₀-, -NR₁₀-C(O)-O-, -NR₁₀-C(O)-NR₁₀-, -S(O)₂-NR₁₀-, -NR₁₀-S(O)₂- or -NR₁₀-S(O)₂-NR₁₀-;

25 each R₅ is independently selected from -H, -Ar₁, -C(O)-Ar₁, -S(O)₂-Ar₁, -R₉, -C(O)-NH₂, -S(O)₂-NH₂, -C(O)-R₉, -C(O)-O-R₉, -S(O)₂-R₉, -C(O)-N(R₁₀)(Ar₁), -S(O)₂-N(R₁₀)(Ar₁), -C(O)-N(R₁₀)(R₉), or -S(O)₂-N(R₁₀)(R₉);

each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted with -OH, -F,

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=O or Ar₁, wherein any R₉ may be substituted with a maximum of two Ar₁;

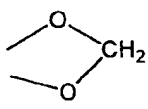
each R₁₀ is independently selected from -H or C₁₋₆ straight or branched alkyl;

5 R₁₃ is -H, -Ar₁, -R₉, -T₁-R₉ or -(CH₂)₁₋₃-T₁-R₉;

each Ar₂ is a cyclic group independently selected from a monocyclic, bicyclic or tricyclic aryl group containing 6, 10, 12 or 14 carbon atoms; a monocyclic, bicyclic or tricyclic cycloalkyl group containing between
10 3 and 15 carbon atoms, said cycloalkyl group being optionally benzofused; or a monocyclic, bicyclic or tricyclic heterocycle group containing between 5 and 15 ring atoms and at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, or -NH-, wherein said
15 heterocycle group optionally contains one or more double bonds and optionally comprises one or more aromatic rings;

Ar₃ is a cyclic group selected from phenyl, a 5-membered heteroaromatic ring or a 6-membered
20 heteroaromatic ring, wherein said heteroaromatic rings comprise from 1-3 heteroatom groups selected from -O-, -S-, -SO-, -SO₂-, =N-, or -NH-;

wherein each Ar₁ or Ar₃ is optionally singly or multiply substituted at any ring atom by -NH₂, -C(O)-OH,
25 -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃

alkyl,  or -Q₁; and

each Q₁ is independently selected from -Ar₁, -R₉, -T₁-R₉, or (CH₂)₁₋₃-T₁-R₉; provided that when -Ar₁ is substituted with a Q₁ which comprises one or more
30 additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁.

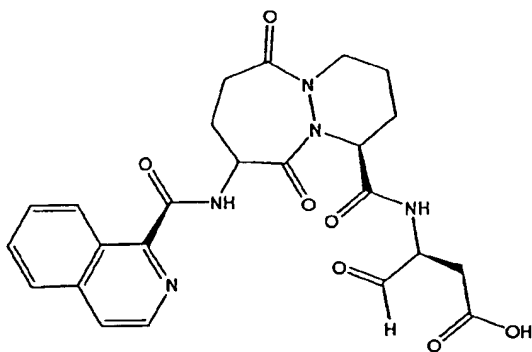
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Preferably, the process of this invention is used as a step in the synthesis of a compound of formula I, wherein n is 1 and m is 2.

In another preferred embodiment, the process of this invention is used as a step in the synthesis of a compound of formula I, wherein R_5 is an acyl moiety selected from $-C(O)-Ar_1$, $-C(O)-NH_2$, $-C(O)-R_9$, $-C(O)-O-R_9$, $-C(O)-N(R_{10})(Ar_1)$, or $-C(O)-N(R_{10})(R_9)$.

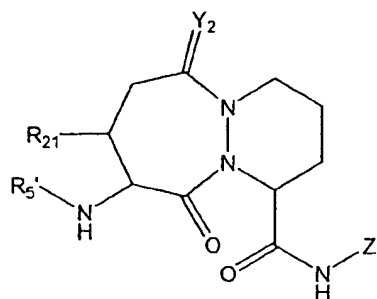
In yet another preferred embodiment, the process of this invention is used as a step in the synthesis of a compound of formula I, wherein X_1 is CH; each J is H; m' is 1; T is $-COOH$ or a biosteric replacement for $-COOH$; g is 0; and R_3 is $-C(O)-R_{13}$.

In the most preferred embodiment of using the process of this invention as a step in the synthesis of a compound of formula I, said compound has the structure:



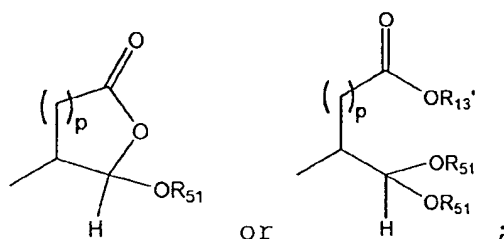
Alternatively, the process of this invention may be used as a step in the synthesis of a compound of the formula (II):

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II; wherein:

Z is selected from



p is 1 or 2;

- 5 each $R_{5'}$ is independently selected from $-C(O)-R_{13'}$, $-C(O)O-R_{9'}$, $-C(O)-N(R_{10'}) (R_{10'})$, $-S(O)_2-R_{9'}$, $-S(O)_2-NH-R_{10'}$, $-C(O)-CH_2-O-R_{9'}$, $-C(O)C(O)-R_{10'}$, $-R_{9'}$, $-H$, $-C(O)C(O)-OR_{10'}$, or $-C(O)C(O)-N(R_{9'}) (R_{10'})$;

- 10 each $R_{9'}$ is independently selected from $-Ar_1$ or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_1 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

- 15 each $R_{10'}$ is independently selected from $-H$, $-Ar_1$, a $-C_{3-6}$ cycloalkyl group, or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3' , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

$R_{13'}$ is selected from H , Ar_1 , or a C_{1-6} straight or branched alkyl group optionally substituted with Ar_1 , $-CONH_2$, $-OR_{5'}$, $-OH$, $-OR_{9'}$, or $-CO_2H$;

- 20 each R_{51} is independently selected from $R_{9'}$, $-C(O)-R_{9'}$, $-C(O)-N(H)-R_{9'}$, or two R_{51} taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing $-O-$, $-S-$, or $-NH-$;

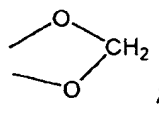
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each R_{21} is independently selected from -H or a $-C_{1-6}$ straight or branched alkyl group;

Y_2 is $-H_2$ or $=O$

each Ar_1 is a cyclic group independently selected
 5 from the set consisting of an aryl group which contains
 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
 and an aromatic heterocycle group containing between 5
 and 15 ring atoms and between 1 and 3 rings, said
 heterocyclic group containing at least one heteroatom
 10 group selected from -O-, -S-, -SO-, SO_2 , $=N-$, and $-NH-$,
 said heterocycle group optionally containing one or more
 double bonds, said heterocycle group optionally
 comprising one or more aromatic rings, and said cyclic
 group optionally being singly or multiply substituted by
 15 $-Q_1$;

each Q_1 is independently selected from the group
 consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$,
 $=O$, $-OH$, -perfluoro C_{1-3} alkyl, $R_{5'}$, $-OR_{5'}$, $-NHR_{5'}$, $OR_{9'}$,

$-N(R_{9'})(R_{10'})$, $R_{9'}$, $-C(O)-R_{10'}$, and  ;

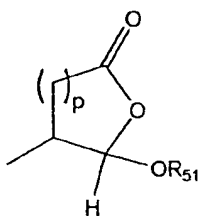
20 provided that when $-Ar_1$ is substituted with a Q_1
 group which comprises one or more additional $-Ar_1$ groups,
 said additional $-Ar_1$ groups are not substituted with
 another $-Ar_1$.

Preferably, the process of this invention is
 25 used as a step in the synthesis of a compound of formula
 II, wherein Y_2 is O and R_{21} is H.

In another preferred embodiment, the process of
 this invention is used as a step in the synthesis of a
 compound of formula II, wherein $R_{5'}$ is selected from
 30 $-C(O)-R_{10'}$, $-C(O)O-R_{9'}$, $-C(O)-N(R_{10'})(R_{10'})$, $-C(O)-CH_2-O-R_{9'}$,
 $-C(O)C(O)-R_{10'}$, $-C(O)C(O)-OR_{10'}$, or $-C(O)C(O)-N(R_{9'})(R_{10'})$.

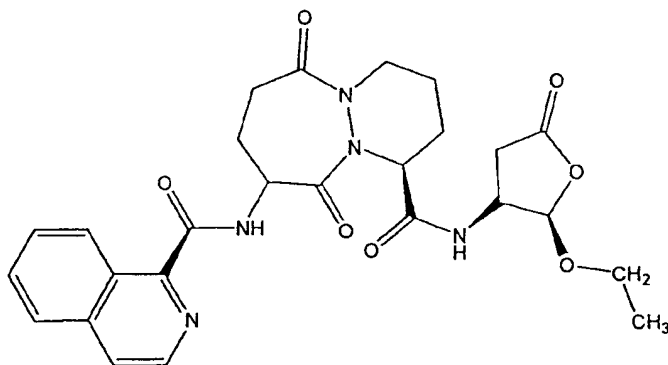
-18-

In yet another preferred embodiment, the process of this invention is used as a step in the synthesis of a compound of formula II, wherein Z is



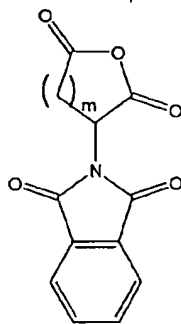
5 ; p is 1 and R₅₁ is selected from -Ar₁, -C₁₋₆ straight or branched alkyl or -C₁₋₆ straight or branched alkyl substituted with Ar₁.

In the most preferred embodiment of using the process of this invention as a step in the synthesis of a compound of formula II, said compound has the structure:



10

In the synthesis of these inhibitors, the terminal carbon of R₁ adjacent the -COOH moiety contains a protecting substituent. Preferably that protecting



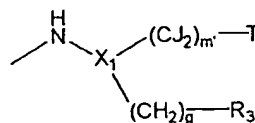
substituent is

15

The synthesis steps from compound H to the inhibitors set forth above involve removal of the

-19-

protecting substituent on R_1 ; coupling of the R_5 -NH- or R_5 -NH- moiety in its place; hydrolysis of the R_2 group;



and coupling of the amine (

in its place.

5 The removal of the protecting substituent on R_1 is typically carried out with hydrazine. The subsequent coupling of the R_5 -NH- or R_5 -NH- moiety is achieved with standard coupling reagents, such as EDC, DCC or acid chloride.

10 Depending upon the nature of R_2 , its hydrolysis may be achieved with an acid (when R_2 is t-butyl), a hydroxide (when R_2 is any other alkyl, alkenyl or alkynyl or Ar) or hydrogenolysis (when R_2 is an Ar-substituted alkyl, alkenyl or alkynyl). This produces the
15 corresponding acid from the ester.

 The acid is then coupled to the amine with standard coupling reagents, such as EDC, DCC or acid chloride.

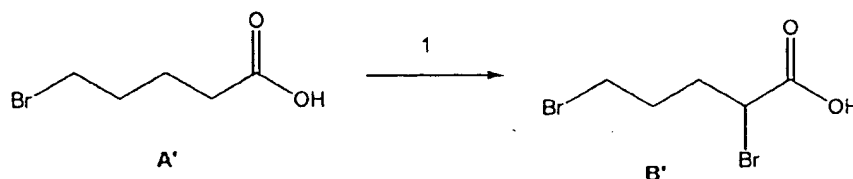
 In order that this invention be more fully
20 understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

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EXAMPLE 1Synthesis of a 7,6 Scaffold for a Caspase Inhibitor

A.



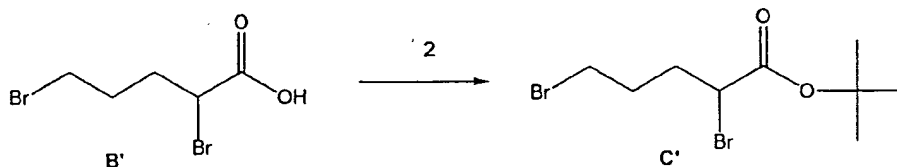
5

Compound A' was dissolved in 5 equivalents of SOCl_2 and then heated to 80°C for 1 hour. The solution was then cooled to 50°C and 2 equivalents of bromine were added. The solution was incubated at 50°C for an additional 12 hours until the red color disappeared. We then cooled the solution to 10°C and added 4 volumes of water. The solution was then re-heated to 50°C for another hour. We then separated the organic and aqueous layer, washed the organic layer consecutively with water, Na_2SO_3 and then brine, removing the aqueous layer after each washing. The final organic layer was then isolated, dried over Na_2SO_4 and concentrated to produce compound B' as an amber oil.

10

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B.



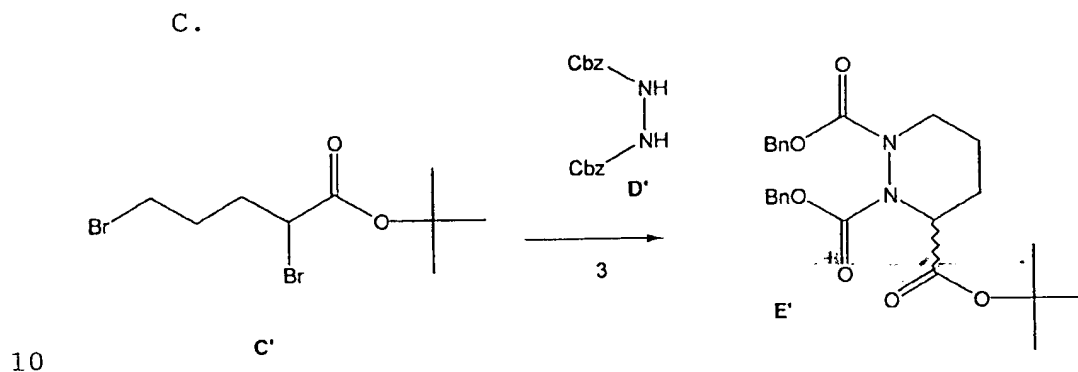
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Compound B' was treated with 1 equivalent of *tert*-butanol and 0.1 equivalents of 4-(dimethylamino)-pyridine in a solution of and the resulting solution cooled to 7°C . We then added a solution of 1 equivalent of DCC in toluene while maintaining reaction temperature at less than 22°C . The cooling bath was removed and the

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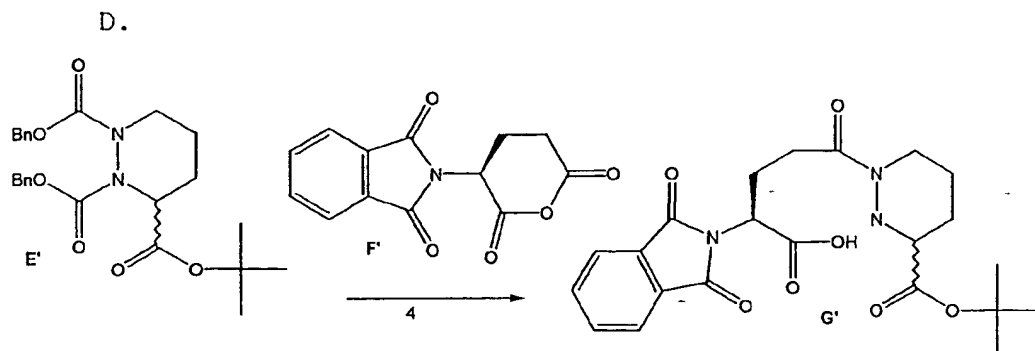
reaction was stirred at ambient temperature under a nitrogen atmosphere for 16 hours. The reaction mixture was then diluted with hexane and cooled to 9°C. The resulting solids were removed by filtration. The
5 filtrate was washed consecutively with 0.1N HCl, water, and then sodium bicarbonate. The filtrate was then dried over sodium sulfate and concentrated *in vacuo* to afford compound C' as a yellow oil.



Compound D' was combined with 1.2 equivalents of compound C' and dissolved in DMF at ambient temperature under nitrogen atmosphere. We then added granular sodium sulfate, 2.5 equivalents of LiOH
15 monohydrate, and then 0.1 equivalents Bu₄NI to the resulting solution. The reaction temperature was maintained at between 20°C and 30°C and allowed to stir for 16 hours. The reaction mixture was then diluted with ethyl acetate and water and the layers separated. The
20 organic layer was washed with water and then brine, dried over sodium sulfate and concentrated *in vacuo* to produce an amber oil. This oil was then dissolved in 5 volumes of ethanol at ambient temperature. We then added 2.5 volumes of water. The resulting mixture was allowed to
25 stir until a white solid formed (approximately 5 hours).

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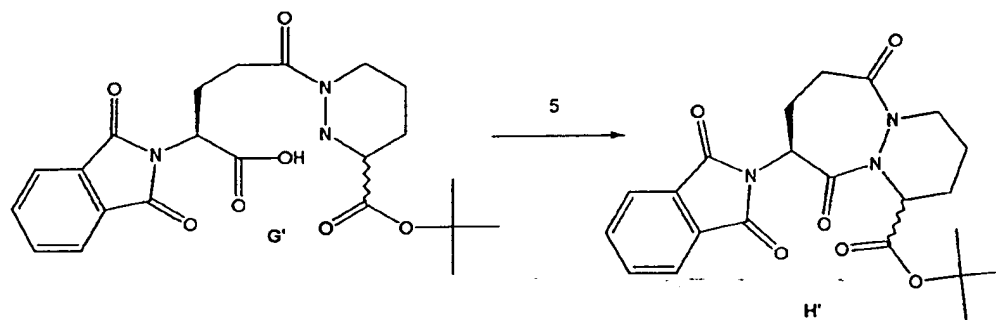
The crystallized product was isolated via filtration then dried *in vacuo* to afford compound E' as a white solid.



We dissolved compound E' in THF. We then added, at ambient temperature under a nitrogen atmosphere, 0.02 equivalents of triethylamine and 0.01 equivalents of $\text{Pd}(\text{OAc})_2$. A solution of 2.5 equivalents of triethylsilane (Et_3SiH) in THF was then added and the resulting black solution was allowed to stir for 16 hours to complete the reaction. We then added a saturated, aqueous solution of sodium bicarbonate followed by a solution of compound F' in THF. After 30 minutes, the layers were separated and the aqueous layer acidified to pH 4.5 with aqueous citric acid. The product in the aqueous layer was then extracted into ethyl acetate. The organic layer was isolated, washed with brine, dried over sodium sulfate and concentrated *in vacuo* to produce a white foam. This crude product was then recrystallized from MTBE to afford compound G' as a white powder.

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E.

Method #1:

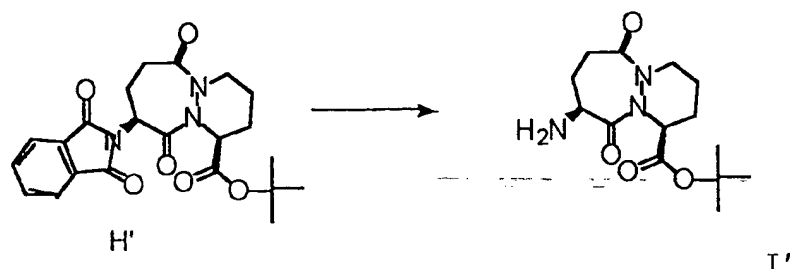
To a suspension of compound G' and 0.1
5 equivalents of DMF in dichloroethane, at 70°C we added 5
equivalents of 2,6-lutidine simultaneously with 2.5
equivalents of SOCl₂ over a period of 3 hours. The
reaction was then diluted with toluene and washed
consecutively with NaHCO₃ and brine. The solution was
10 then dried over Na₂SO₄ and concentrated *in vacuo* to afford
compound H' as a yellow solid.

Method #2:

To a suspension of compound G' in
15 dichloroethane, at 70°C, we added 4 equivalents of 2,6-
lutidine followed by 2 equivalents of methanesulfonyl
chloride. The resulting solution was stirred at 70°C for
12 hours. The reaction was then diluted with toluene and
washed consecutively with NaHCO₃ and brine. The solution
20 was then dried over Na₂SO₄ and concentrated *in vacuo* to
afford compound H' as a white solid. Method #2 produced
a significantly higher yield of H' as compared to Method
#1.

EXAMPLE 2Use of Intermediate H' to Produce an Inhibitor of ICE

A.



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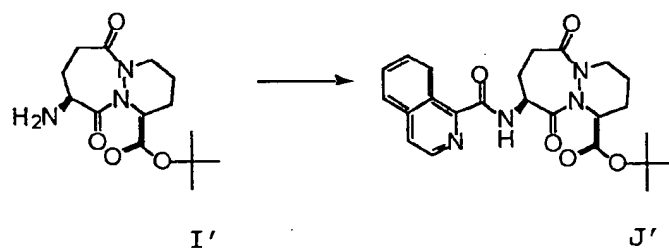
t-Butyl-9-amino-6, 10-dioxo-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxylate (GB 2,128,984) To a suspension of H' (107 g, 0.25 mol) in ethanol (900 mL) was added hydrazine (27 mL, 0.55 mol) and the resulting mixture was allowed to stir at ambient temperature. After 4 hours, the reaction was concentrated in vacuo and the resulting white solid was suspended in acetic acid (1L of 2N) and allowed to stir at ambient temperature for 16 hours. The resulting white solid was filtered off and washed with water. The filtrate was made basic by the addition of solid sodium carbonate and the product extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo to afford 79 mg of compound I' as a yellow viscous oil.

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B.



I'

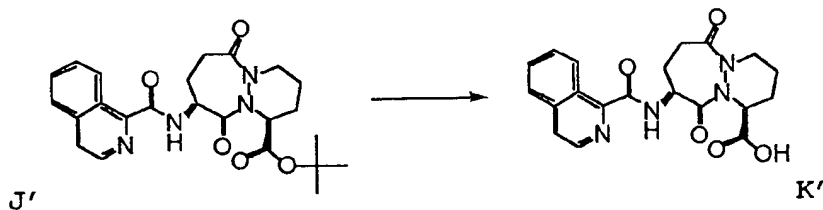
J'

-25-

t-Butyl-9-(isoquinolin-1-oylamino) -6, 10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]
diazepine-1-carboxylate To a solution of the amine I' (79
g, 0.265 mol) and isoquinolin-1-carboxylic acid (56g,
5 0.32 mol) in dichloromethane:DMF (400mL:400mL) was added
hydroxybenztriazole (54 g, 0.4 mol) and 1-(3-
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
(74 g, 0.39 mol) and the resulting mixture was allowed to
stir at ambient temperature for 16 hours. The reaction
10 mixture was poured into water and extracted with ethyl
acetate. The ethyl acetate layer was washed with 0.5N
sodium bisulfate, water, sodium bicarbonate, brine, dried
over sodium sulfate and concentrated *in vacuo* to afford
122 g of compound J' as an orange solid-foam.

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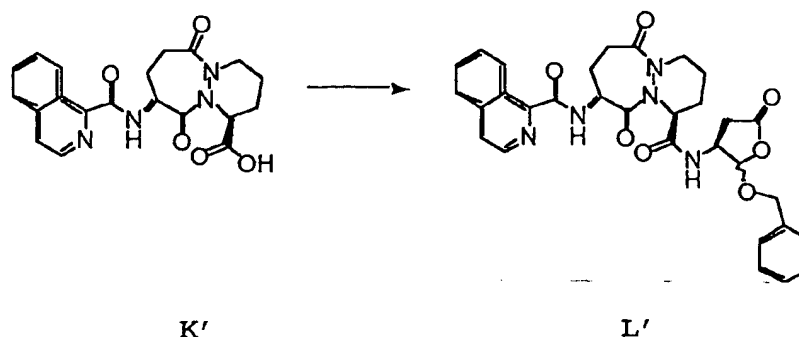
C.



9-(isoquinolin-1-oylamino) -6, 10-dioxo-1,2,3,4,7,8,9,10-
octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-
carboxylate A solution of the ester J' (122 g) in
20 dichloromethane and trifluoroacetic acid (200 mL) was
allowed to stir at ambient temperature for 16 hours. The
reaction mixture was concentrated to a black oil which
was then triturated with acetonitrile and ether to afford
98 g of compound K' as a pale yellow solid.

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D.



[1S, 9S (2RS, 3S)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-ylamino)-
 5 1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide To a solution of (3S, 2RS) 3-allyloxycarbonylamino-2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran [Bioorg. & Med. Chem. Lett., 2, pp.
 10 615-618 (1992)] (4.4 g, 15.1 mmol) in dichloromethane was added N,N-dimethylbarbituric acid (5.9g, 3.8 mmol) then tetrakis(palladium(0) triphenyl phosphine (1.7 g, 1.5 mmol) and the resulting mixture was allowed to stir at ambient temperature for 15 minutes. To the resulting
 15 mixture was added the acid, compound K' (5.0 g, 12.6 mmol), hydroxybenztriazole(2.0 g, 14.8 mmol) then and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.7g, 14 mmol) and the reaction was allowed to stir for 3 hours at ambient temperature. The reaction mixture was
 20 then poured into water and extracted with ethyl acetate. The organics were washed with 0.5M sodium bisulfate, water, sodium bicarbonate, brine, dried over magnesium sulfate and concentrated in vacuo to afford 2.6 g of the crude product as a yellow foam. The crude material was
 25 purified by column chromatography (SiO₂, dichloromethane:acetone 9:1 - 3:1) to afford 1.2 g of the compound L'.

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Compound L' and related compounds that may be synthesized using the method of this invention as an intermediate step are described in WO 97/22619, the disclosure of which is herein incorporated by reference.

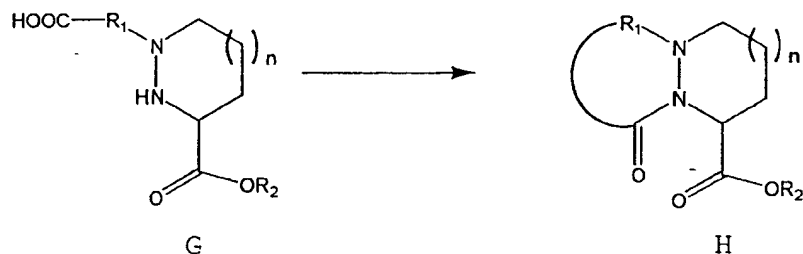
5 Those related compounds may be synthesized from the product of the method of this invention, H or H', through
--- modifications of the procedure set forth in Example 2.
Such modifications are well known in the art.

While we have hereinbefore presented a number
10 of embodiments of this invention, it is apparent that my basic construction can be altered to provide other embodiments which utilize the methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the claims appended hereto
15 rather than the specific embodiments which have been presented hereinbefore by way of example.

CLAIMS

We claim:

1. A process for converting compound G to compound H:



wherein:

R_1 is a C2-C4 straight chain alkyl optionally substituted at any carbon with one or more substituents selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl or alkynyl, oxo, halo, NO_2 , $\text{N}(\text{R}_4)(\text{R}_4)$, CN, Ar or O-Ar;

R_2 is selected from hydrogen, C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, C1-C6 alkyl or Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar;

n is 0 or 1;

Ar is a saturated, partially saturated or unsaturated monocyclic or bicyclic ring structure, wherein each ring contains 5 to 7 ring atoms and each ring optionally contains from 1 to 3 heteroatoms selected from O, N and S;

wherein Ar is optionally substituted at one or more ring atoms with one or more substituents independently selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl

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or alkynyl, oxo, halo, NO₂, N(R₄)(R₄), CN, Ar₁, O-Ar₁;
wherein

Ar₁ is a saturated, partially saturated or unsaturated monocyclic or bicyclic ring structure, wherein each ring contains 5 to 7 ring atoms and each ring optionally contains from 1 to 3 heteroatoms selected from O, N and S; and

each R₄ is independently selected from H or an amino protecting group, with the proviso that both R₄ are not simultaneously hydrogen, said process comprising the steps of:

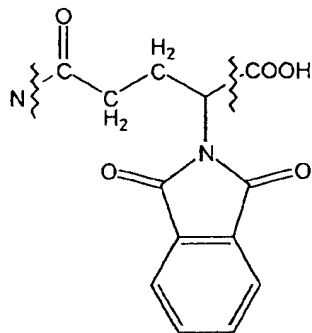
- (a) suspending compound G in an organic solvent selected from dichloroethane, dichloromethane, toluene, chlorobenzene, chloroform, monoglyme, diglyme or CCl₄;
- (b) adjusting the temperature of the resulting solution to between 20°C and 100°C;
- (c) adding 2 to 4 equivalents of base and more than about 1 equivalent of RSO_pCl_p to said solution, wherein R is absent or selected from C1-C6 straight or branched alkyl or Ar, and each p is independently 1 or 2; and
- (d) incubating said solution over a period of between 2 and 18 hours.

2. The process according to claim 1, wherein R₁ is substituted at the terminal carbon bound to the COOH moiety with a nitrogen-containing moiety that can be chemically modified to an amine.

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3. The process according to claim 2, wherein

R₁ is:



4. The process according to claim 1, wherein

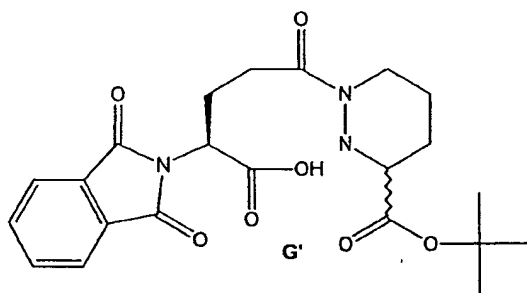
n is 1.

5. The process according to claim 1, wherein

R₂ is t-butyl.

6. The process according to claim 5, wherein

compound G has the formula:



7. The process according to claim 1, wherein

in step (a) the organic solvent is dichloroethane.

8. The process according to claim 1, wherein

step (b) is carried out at about 70°C.

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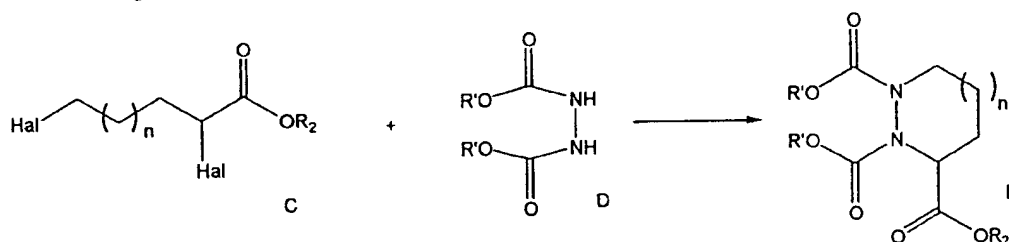
9. The process according to claim 1, wherein in step (c) about 2 equivalents of RSO_pCl_p are used.

10. The process according to claim 9, wherein RSO_pCl_p is methanesulfonyl chloride or SOCl_2 .

11. The process according to claim 1, wherein said base is selected from pyridine, collidine, lutidine, NaHCO_3 , imidazole, triethylamine, N-methylmorpholine, diisopropylethylamine or K_2CO_3 .

12. The process according to claim 11, wherein said base is 2,6-lutidine.

13. A process for producing compound E by reacting compounds C and D:



comprising the steps of:

- a) dissolving compounds C and D together in DMF;
- b) adding to said solution of C and D:
 - i) a water scavenger;
 - ii) a metal hydroxide selected from LiOH , NaOH or KOH ; and
 - iii) a phase transfer catalyst
- c) allowing the mixture produced in step b) to react at room temperature for 2 to 48 hours;

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- d) adding an organic solvent and water to said mixture to create an aqueous phase and an organic phase; and
 - e) purifying compound E from said organic phase;
- wherein:

R_2 is selected from hydrogen, C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl C1-C6 alkyl or Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar;

n is 0 or 1;

"Hal" is any halogen; and

each R' is an independently selected carboxyl protecting group.

14. The process according to claim 13, wherein said water scavenger is sodium sulfate.

15. The process according to claim 13, wherein said metal hydroxide is LiOH.

16. The process according to claim 13, wherein said phase transfer catalyst is Bu_4NI .

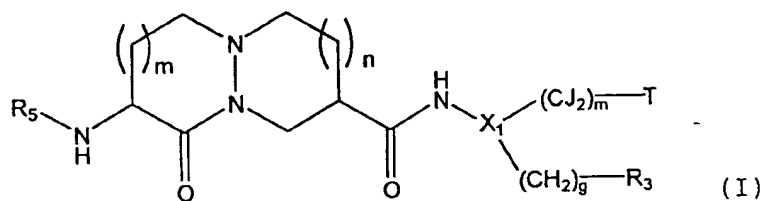
17. The process according to claim 13, wherein n is 1.

18. The process according to claim 13, wherein each Hal is Br.

19. The process according to claim 13, wherein R_2 is t-butyl.

20. The process according to claim 13, wherein R' is benzyl.

21. The process according to claim 1 or 13, wherein said process is used as a step in the synthesis of a compound (I) having the formula:



wherein:

any ring is optionally substituted at any carbon by Q₁, at any nitrogen by R₅, and at any atom by =O, -OH, -COOH, or halogen;

X₁ is CH or N;

g is 0 or 1;

m is 0, 1 or 2;

n is 0 or 1;

each J is independently selected from -H, -OH, or -F, provided that when a first and a second J are bound to a C, and said first J is -OH, then said second J is -H;

T is -Ar₃, -OH, -CF₃, -C(O)-C(O)-OH, -C(O)-OH or any biosteric replacement for -C(O)-OH;

R₃ is -CN, -CH=CH-R₉, CH=N-O-R₉, -(CH₂)₁₋₃-T₁-R₉, -CJ₂-R₉, -C(O)-R₁₃, or -C(O)-C(O)-N(R₅)(R₁₀);

T₁ is -CH=CH-, -O-, -S-, -SO-, -SO₂-, -NR₁₀-, -NR₁₀-C(O)-, -C(O)-, -O-C(O)-, -C(O)-O-, -C(O)-NR₁₀-, O-C(O)-NR₁₀-, -NR₁₀-C(O)-O-, -NR₁₀-C(O)-NR₁₀-, -S(O)₂-NR₁₀-, -NR₁₀-S(O)₂- or -NR₁₀-S(O)₂-NR₁₀-;

each R₅ is independently selected from -H, -Ar₁, -C(O)-Ar₁, -S(O)₂-Ar₁, -R₉, -C(O)-NH₂, -S(O)₂-NH₂, -C(O)-R₉,

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-C(O)-O-R₉, -S(O)₂-R₉, -C(O)-N(R₁₀)(Ar₁),
 -S(O)₂-N(R₁₀)(Ar₁), -C(O)-N(R₁₀)(R₉), or
 -S(O)₂-N(R₁₀)(R₉);

each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, =O or Ar₁, wherein any R₉ may be substituted with a maximum of two Ar₁;

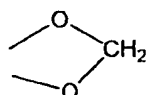
each R₁₀ is independently selected from -H or C₁₋₆ straight or branched alkyl;

R₁₃ is -H, -Ar₁, -R₉, -T₁-R₉ or -(CH₂)₁₋₃-T₁-R₉;

each Ar₁ is a cyclic group independently selected from a monocyclic, bicyclic or tricyclic aryl group containing 6, 10, 12 or 14 carbon atoms; a monocyclic, bicyclic or tricyclic cycloalkyl group containing between 3 and 15 carbon atoms, said cycloalkyl group being optionally benzofused; or a monocyclic, bicyclic or tricyclic heterocycle group containing between 5 and 15 ring atoms and at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, or -NH-, wherein said heterocycle group optionally contains one or more double bonds and optionally comprises one or more aromatic rings;

Ar₃ is a cyclic group selected from phenyl, a 5-membered heteroaromatic ring or a 6-membered heteroaromatic ring, wherein said heteroaromatic rings comprise from 1-3 heteroatom groups selected from -O-, -S-, -SO-, -SO₂-, =N-, or -NH-;

wherein each Ar₁ or Ar₃ is optionally singly or multiply substituted at any ring atom by -NH₂, -C(O)-OH, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃

alkyl,  or -Q₁; and

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each Q_1 is independently selected from $-Ar_1$, $-R_9$, $-T_1-R_9$, or $(CH_2)_{1-3}-T_1-R_9$; provided that when $-Ar_1$ is substituted with a Q_1 which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 .

22.- The process according to claim 21, wherein m is 2 and n is 1.

23. The process according to claim 22, wherein the terminal R_5 is selected from $-C(O)-Ar_1$, $-C(O)-NH_2$, $-C(O)-R_9$, $-C(O)-O-R_9$, $-C(O)-N(R_{10})(Ar_1)$, or $-C(O)-N(R_{10})(R_9)$.

24. The process according to claim 23, wherein:

X_1 is CH ;

each J is H ;

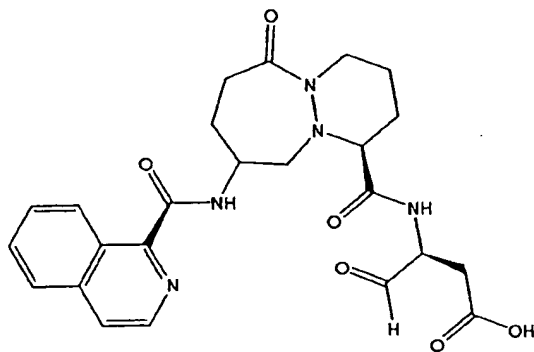
m' is 1;

T is $-COOH$ or a biosteric replacement for $-COOH$;

g is 0; and

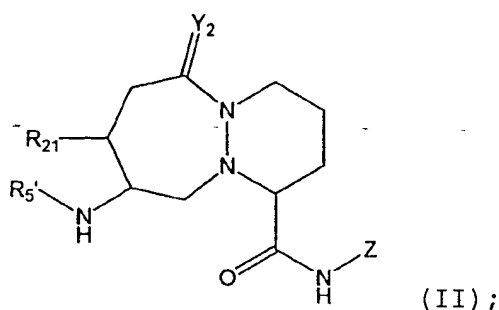
R_3 is $-C(O)-R_{13}$.

25. The process according to claim 21, wherein compound I has the structure:



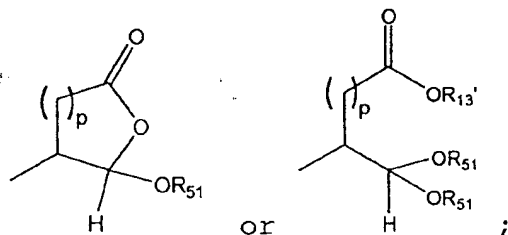
-36-

26. The process according to claim 4 or 17, wherein said process is used as a step in the synthesis of a compound of the formula (II):



wherein:

Z is selected from



p is 1 or 2;

each $R_{5'}$ is independently selected from $-C(O)-R_{10'}$, $-C(O)O-R_{9'}$, $-C(O)-N(R_{10'})(R_{10'})$, $-S(O)_2-R_{9'}$, $-S(O)_2-NH-R_{10'}$, $-C(O)-CH_2-O-R_{9'}$, $-C(O)C(O)-R_{10'}$, $-R_{9'}$, $-H$, $-C(O)C(O)-OR_{10'}$, or $-C(O)C(O)-N(R_{9'})(R_{10'})$;

each $R_{9'}$ is independently selected from $-Ar_1$ or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_1 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each $R_{10'}$ is independently selected from $-H$, $-Ar_1$, a $-C_{3-6}$ cycloalkyl group, or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

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R_{13} is selected from H, Ar_1 , or a C_{1-6} straight or branched alkyl group optionally substituted with Ar_1 , $-CONH_2$, $-OR_{5'}$, $-OH$, $-OR_{9'}$, or $-CO_2H$;

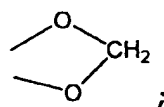
each R_{51} is independently selected from $R_{9'}$, $-C(O)-R_{9'}$, $-C(O)-N(H)-R_{9'}$, or two R_{51} taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing $-O-$, $-S-$, or $-NH-$;

each R_{21} is independently selected from $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

Y_2 is $-H_2$ or $=O$

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$; and

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, $R_{5'}$, $-OR_{5'}$, $-NHR_{5'}$, $OR_{9'}$,

$-N(R_{9'}) (R_{10'})$, $R_{9'}$, $-C(O)-R_{10'}$, and  ;

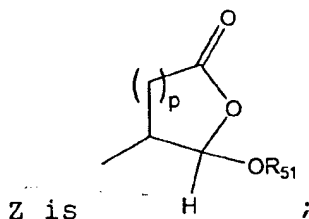
provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with another $-Ar_1$.

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27. The process according to claim 26, wherein in compound II, Y_2 is O and R_{21} is H.

28. The process according to claim 26, wherein in compound II, $R_{5'}$ is selected from $-C(O)-R_{10'}$, $-C(O)O-R_{9'}$, $-C(O)-N(R_{10'})(R_{10'})$, $-C(O)-CH_2-O-R_{9'}$, $-C(O)C(O)-R_{10'}$, $-C(O)C(O)-OR_{10'}$, or $-C(O)C(O)-N(R_{9'})(R_{10'})$.

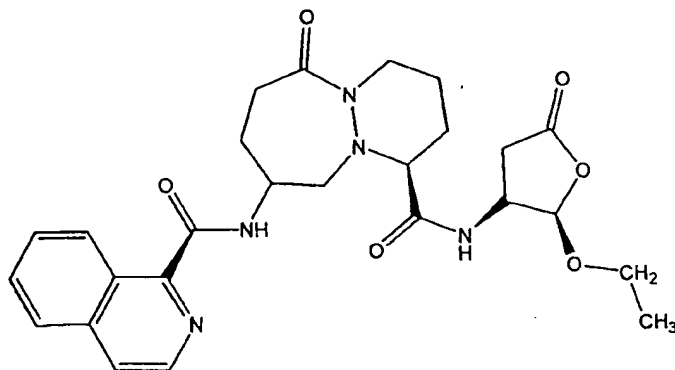
29. The process according to claim 26, wherein in compound II,



p is 1; and

R_{51} is selected from $-Ar_1$, $-C_{1-6}$ straight or branched alkyl or $-C_{1-6}$ straight or branched alkyl substituted with Ar_1 .

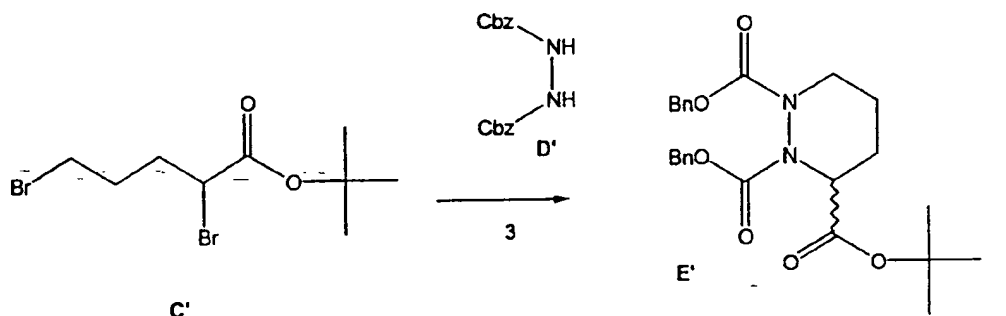
30. The process according to claim 26, wherein compound II has the structure:



31. The process according to claim 30, comprising the steps of:

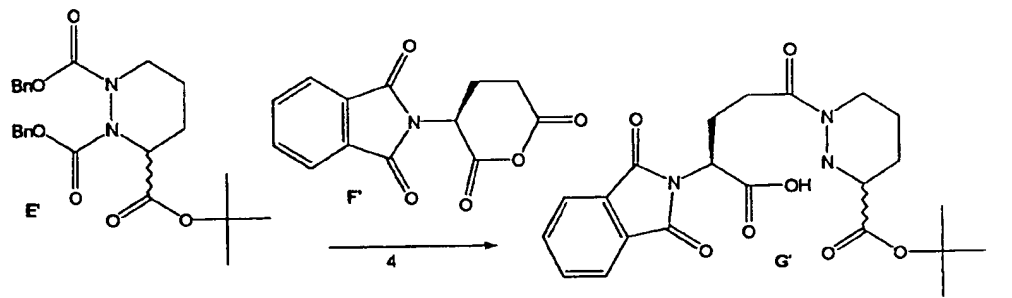
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a) reacting compound C' and compound D' together in DMF in the presence of sodium sulphate, LiOH and Bu₄NI and in the absence of oxygen to produce compound E':



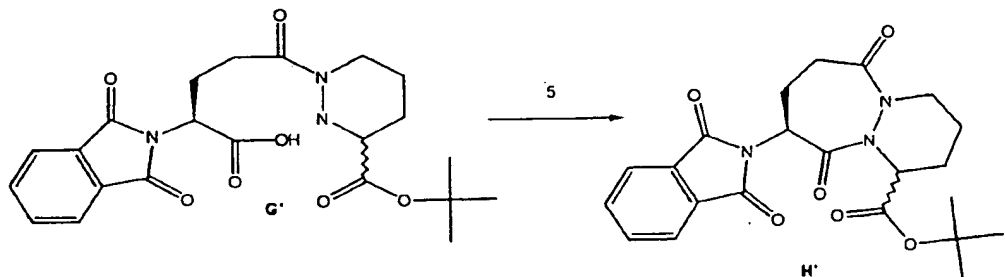
b) dissolving E' in THF in the absence of oxygen, adding triethylamine and Pd(OAc)₂, and allowing reaction to proceed for 12 to 24 hours;

c) adding to said solution produced in step b) aqueous sodium bicarbonate and compound F' to produce compound G':



and

d) suspending compound G' in dichloroethane at between 50°C and 80°C, and adding 2,6-lutidine and methanesulfonyl chloride to produce compound H':



INTERNATIONAL SEARCH REPORT

Inter: national Application No

PCT/US 99/19080

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D237/04 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 4 692 438 A (HASSALL ET. AL.) 8 September 1987 (1987-09-08) column 3, line 65 -column 4, line 12; example 1	1-12
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/19080

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 95 35308 A (VERTEX PHARMACEUTICALS INC.) 28 December 1995 (1995-12-28) cited in the application page 80 -page 83 page 169 -page 173; claims 110,111 -----	1-31

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